

# INSECT STING ALLERGY

ALL 1.3

Includes Bee, Wasp, Ant, and Other Insect Sting Allergy.

## INFORMATION REQUIRED *Any history.*

### All Applicants:

- Report of Medical Examination to include the following:
  - Insect(s) to which allergic
  - Date of last reaction
  - Description of reaction to include description of angioedema and symptoms associated with respiratory or cardiovascular compromise.
  - Severity of reaction
  - Treatment to include resuscitative or life-support treatment, and immunotherapy, if required.
  - Atopic history, i.e., triad of asthma, rhinitis, and chronic urticaria.
  - Recommendations for follow-up over the next 3 years.

### Applicants With a History of Immunotherapy:

- Copy of immunotherapy report to include initiation and termination dates.

### If Applicable:

- Copy of skin tests, venom challenge tests, and other diagnostic test reports.
- Copy of discharge summary for *all* related emergency room visits and hospitalizations.

CLEARANCE CRITERIA	REVIEWER	GUIDANCE
<ol style="list-style-type: none"> <li>1. Local reaction only. May include local erythema (redness), edema (swelling), or ecchymosis (bruising).</li> <li>2. Mild or self-limited allergic reaction. Reaction <i>may include</i> one or more of the following symptoms: urticaria (hives), rash, pruritis (itching), flushing, or other hypersensitivity reaction, e.g., mild GI symptoms.</li> <li>3. If reaction includes angioedema, edema does <i>not</i> cause airway obstruction, i.e., does <i>not</i> involve the neck, oropharynx (tongue, soft palate, lips), or larynx.</li> <li>4. No significant circulatory (hypotension, syncope, shock) or respiratory (wheezing, SOB) compromise.</li> <li>5. No anaphylactoid reaction or anaphylaxis, i.e., severe life-threatening allergic reaction.</li> <li>6. No resuscitative or life support treatment required.</li> <li>7. No coexisting atopy, i.e., triad of asthma, rhinitis, and chronic urticaria.</li> </ol>		
<b>Meets clearance criteria 1-7, AND</b> <ul style="list-style-type: none"> <li>• No, or completed course, of immunotherapy.</li> </ul>	RN	<b>CLEAR</b>  PCMO FOLLOW-UP Anaphylaxis kit required.
<b>Does not meet clearance criteria due to one or more of the following:</b> <ul style="list-style-type: none"> <li>• Ongoing immunotherapy.</li> </ul>	RN	<b>DEFER</b>  Until immunotherapy complete.  PCMO FOLLOW-UP Anaphylaxis kit required.
<b>Does not meet clearance criteria due to one or more of the following:</b> <ul style="list-style-type: none"> <li>• Reaction includes angioedema <i>with</i> associated airway obstruction, i.e., edema involves the neck, oropharynx (tongue, soft palate, lips), or larynx.</li> <li>• Coexisting atopy, i.e., triad of asthma, rhinitis, and chronic urticaria.</li> </ul>	MED ADVISOR	Risk varies - assess based on detailed history.

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<p><b>Does not meet clearance criteria due to one or more of the following:</b></p> <ul style="list-style-type: none"> <li>• Reaction is severe or life-threatening (anaphylactoid or anaphylaxis), i.e., includes any of the following symptoms: <ul style="list-style-type: none"> <li>- Significant respiratory compromise (bronchospasm, stidor, dyspnea, apnea) .</li> <li>- Significant cardiovascular compromise (hypotension, syncope, shock).</li> <li>- Loss of consciousness.</li> </ul> </li> <li>• Resuscitative or life support treatment required.</li> </ul>	<p style="text-align: center;"><b>MED ADVISOR</b></p>	<p style="text-align: center;"><b>DEFER/MNQ</b></p>
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### DIAGNOSTIC CODES

989.5 Bee Sting (anaphylactic shock)  
989.5 Insect Bite (venomous, poisoning)

Cross Reference ICD.9.CM

### NOTES AND INSTRUCTIONS FOR REVIEWERS:

**Reviewers to Consider:**

- None

### COMMENTS:

#### Definitions:

- **Anaphylaxis:** Immediate systemic reaction caused by rapid IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils. Clinically, the term anaphylaxis is used to describe a rapidly developing generalized reactions that may include pruritis, urticaria, angioedema (especially laryngeal edema), hypotension, wheezing and bronchospasm, nausea, vomiting, pain, diarrhea, uterine contractions, and/or direct cardiac effects, including arrhythmias.
- **Anaphylactoid reactions:** Immediate systemic reactions that are clinically similar to anaphylactic episodes but are not caused by an IgE-mediated immune response. One of the most common mechanisms of production of anaphylactoid reactions involves the direct (nonantigen-IgE) release of mediators from mast cells and basophils. This occurs in reactions to drugs and biologicals, most cases of idiopathic anaphylaxis, the majority of cases of exercise-induced anaphylaxis, and probably anaphylaxis from other physical factors, such as cold and sunlight. It may also be produced by chemical agents capable of causing mast cell degranulation, e.g., radiocontrast material or opiates.
- **Angioedema:** Edema extending into the deep dermis and subcutaneous tissue. The lesions of angioedema are large plaques (swollen and nonpitting), often on the eyelids, lips, palms, soles, or other parts of the face and extremities. Clinically it is characterized by swelling of the subcutaneous or submucosal tissue but without puritis. Involvement of the mucous membranes or the oropharynx may cause airway obstruction.
- **Urticaria (hives):** Raised, erythematous areas of edema involving only the superficial part of dermis. Urticaria lesions are typically localized, raised, swellings that are intensely itchy.

**Risk of Recurrence:** Major risk factors for recurrence of anaphylaxis include a prior history of such reactions, beta-adrenergic blocker or possibly ACE inhibitor therapy, and the multiple antibiotic sensitivity syndrome. Atopic background may be a risk factor for venom and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to many medications.

*[The diagnosis and management of anaphylaxis. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology 1998 Aug;102(2):264 and 1998]*

**Symptoms:** Evaluation of symptoms should include the upper and lower airways (evidence of edema, stridor, dyspnea, wheezing, or apnea), the cardiovascular system (hypotension or syncope), the skin (urticaria, angioedema, or flushing), the gastrointestinal system (vomiting and diarrhea), and the state of consciousness. Signs and symptoms of potentially



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life-threatening anaphylaxis include stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmia, shock, seizures, and loss of consciousness. Such patients require immediate treatment.

### Frequency of Occurrence of Signs and Symptoms of Anaphylaxis

SIGNS/SYMPTOMS	PERCENT
Urticaria and angioedema	88
Upper airway edema	56
Dyspnea, wheeze	47
Flush	46
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Headache	15
Rhinitis	16
Substernal pain	6
Itch without rash	4.5
Seizure	1.5

**Atopy:** Atopic subjects appear to be predisposed to anaphylaxis and anaphylactoid reactions in general because they account for an inordinate percentage of cases in random series and in series of cases of insect sting anaphylaxis, exercise-induced anaphylaxis, and anaphylactoid reactions to radiocontrast material. It is unclear why atopics exhibit a heightened predisposition. It is evident that increased levels of IgE and IgE mast cell interaction (as conventionally understood) are not sufficient alone to account for this phenomenon. [Middleton: *Allergy: Principles and Practice*, 5th ed., 1998]

**Death from Anaphylaxis:** Is usually due to respiratory obstruction and/or cardiovascular collapse. In patients dying from respiratory obstruction there is edema of the airway and pulmonary hyperinflation. Upper airway edema can be found in about 60% of deaths. Bronchial obstruction with hyperinflation of the lungs occurs in about half the cases. Bronchial obstruction is due to a combination of spasm, submucosal edema, and secretions. When death is due to cardiovascular collapse, there may be no postmortem findings. Myocardial damage, however, can be detected in the majority of cases.

**Insect Stings:** Stinging insects are members of the order Hymenoptera, which includes apids (bees), vespids (yellow jackets, hornets, wasps) and ants. Insect stings commonly cause local (non-anaphylactic) as well as generalized skin, respiratory, and/or vascular reactions. The self-reported prevalence of insect sting allergy is about 0.5-1.0%. About 40 deaths are attributed to insect stings each year in the United States.

Systemic reactions to stings are differentiated from local reactions (e.g., swelling of the area around the sting site in which the signs and symptoms are contiguous with the sting site) and toxic reactions, which occur after multiple stings. Toxic reactions may appear identical to anaphylaxis, but are produced by vasoactive compounds in the venom itself, rather than by compounds released in response to IgE activity. Delayed reactions (>4 hours post-sting) may include a serum sickness-like syndrome, Guillain-Barre syndrome, glomerulonephritis, or myocarditis. The pathophysiology of most delayed reactions is unclear. In adults with a history of insect sting anaphylaxis, the risk of anaphylaxis with future stings is 30-60%, suggesting that hypersensitivity can be lost.

**Diagnosis:** is by clinical history and demonstration of venom-specific IgE antibodies. Skin testing is preferred over in vitro tests because it is more sensitive. Lyophilized preparations are available for testing for honeybee, wasp, yellow jacket, yellow hornet, and white-faced hornet venoms. Whole body extracts are available for testing fire ant and sweatbee sensitivity. Diagnostic studies are not indicated for large local reactions because there is no evidence that these reactions are predictive of later systemic reactions. [Nicklas et al. 1998]

**Fire Ants:** Based on physician surveys, 2-4% of individual have serious systemic anaphylactic reactions to stings by imported fire ants, and 17-56% have large local reactions. Large local reactions may evolve into a second phase of pruritic erythema induration 6-24 hours later.

**Reduviid Bug:** The reduviid bug (*Triatoma spp.*) is a nocturnal blood-sucking arthropod found in the southwest U.S. and in other parts of the world. From serologic studies, the prevalence of IgE-mediated sensitivity is about 6% in areas where the insects are found. Both anaphylactic and local reactions occur, in response to salivary gland antigens deposited in the bite. Other insect bites may also cause a range of allergic reactions. Skin testing is used to confirm the diagnosis of reduviid bug allergy, and subsequent reactions have been prevented by allergen immunotherapy. [Nicklas et al. 1998]

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### Management:

\* **Venom Immunotherapy:** Venom immunotherapy is indicated in adults who have experienced a systemic reaction to an insect sting and who have positive skin test responses to one or more insects. Treatment is recommended for 3-5 years, after which the risk of anaphylaxis is estimated at 8-14%. Guidelines for the safe cessation of venom immunotherapy are still developing. Conversion from two positive skin tests to a negative result is an agreed upon criteria for stopping therapy. Roughly 20% of individuals convert to a negative skin test after 3-5 years of therapy. [*American Journal of Emergency Medicine*, Vol. 14, No. 4, July 1996]

• **Venom Immunotherapy for Fire Ants:** Whole body immunotherapy for fire ants consists of weekly subcutaneous injections, which may continue over a period of years. In patients who discontinued therapy after 2-19 years, 76% still had skin test sensitivity, but 94% had no reaction on receiving a sting.

• **Anaphylaxis and Immunotherapy:** Venom immunotherapy is generally well-tolerated. Approximately 6% of patients have treatment-related allergic reactions to the venom. The reactions tend to be mild and do not require treatment. Severe anaphylactic reactions to skin testing and allergen immunotherapy are rare, but do occur. In a national survey of allergists covering the period 1985-1988, 10% of patients with insect sting allergy who received venom immunotherapy were reported. Sting-sensitive individuals who do not receive venom immunotherapy should be provided instruction on avoidance and use of use of epinephrine as emergency aid.

Literature review and abstract available.



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life-threatening anaphylaxis include stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmia, shock, seizures, and loss of consciousness. Such patients require immediate treatment.

### Frequency of Occurrence of Signs and Symptoms of Anaphylaxis

SIGNS/SYMPTOMS	PERCENT
Urticaria and angioedema	88
Upper airway edema	56
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Rhinitis	16
Substernal pain	6
Itch without rash	4.5
Seizure	1.5

**Atopy:** Atopic subjects appear to be predisposed to anaphylaxis and anaphylactoid reactions in general because they account for an inordinate percentage of cases in random series and in series of cases of idiopathic anaphylaxis, exercise-induced anaphylaxis, and anaphylactoid reactions to radiocontrast material. It is unclear why atopics exhibit a heightened predisposition. It is evident that increased levels of IgE and IgE mast cell interaction (as conventionally understood) are not sufficient alone to account for this phenomenon. [Middleton: *Allergy: Principles and Practice*, 5th ed., 1998]

**Death from Anaphylaxis:** Is usually due to respiratory obstruction and/or cardiovascular collapse. In patients dying from respiratory obstruction there is edema of the airway and pulmonary hyperinflation. Upper airway edema can be found in about 60% of deaths. Bronchial obstruction with hyperinflation of the lungs occurs in about half the cases. Bronchial obstruction is due to a combination of spasm, submucosal edema, and secretions. When death is due to cardiovascular collapse, there may be no postmortem findings. Myocardial damage, however, can be detected in the majority of cases.

**Insect Stings:** Stinging insects are members of the order Hymenoptera, which includes apids (bees), vespids (yellow jackets, hornets, wasps) and ants. Insect stings commonly cause local (non-anaphylactic) as well as generalized skin, respiratory, and/or vascular reactions. The self-reported prevalence of insect sting allergy is about 0.5-1.0%. About 40 deaths are attributed to insect stings each year in the United States.

Systemic reactions to stings are differentiated from local reactions (e.g., swelling of the area around the sting site in which the signs and symptoms are contiguous with the sting site) and toxic reactions, which occur after multiple stings. Toxic reactions may appear identical to anaphylaxis, but are produced by vasoactive compounds in the venom itself, rather than by compounds released in response to IgE activity. Delayed reactions (>4 hours post-sting) may include a serum sickness-like syndrome, Guillain-Barre syndrome, glomerulonephritis, or myocarditis. The pathophysiology of most delayed reactions is unclear. In adults with a history of insect sting anaphylaxis, the risk of anaphylaxis with future stings is 30-60%, suggesting that hypersensitivity can be lost.

**Diagnosis:** is by clinical history and demonstration of venom-specific IgE antibodies. Skin testing is preferred over in vitro tests because it is more sensitive. Lyophilized preparations are available for testing for honeybee, wasp, yellow jacket, and sweatbee sensitivity. Diagnostic studies are not indicated for large local reactions because there is no evidence that these reactions are predictive of later systemic reactions. [Nicklas et al. 1998]

**Fire Ants:** Based on physician surveys, 2-4% of individual have serious systemic anaphylactic reactions to stings by imported fire ants, and 17-56% have large local reactions. Large local reactions may evolve into a second phase of pruritic erythema induration 6-24 hours later.

**Reduviid Bug:** The reduviid bug (*Triatoma spp.*) is a nocturnal blood-sucking arthropod found in the southwest U.S. and in other parts of the world. From serologic studies, the prevalence of IgE-mediated sensitivity is about 6% in areas where the insects are found. Both anaphylactic and local reactions occur, in response to salivary gland antigens deposited in the bite. Other insect bites may also cause a range of allergic reactions. Skin testing is used to confirm the diagnosis of reduviid bug allergy, and subsequent reactions have been prevented by allergen immunotherapy. [Nicklas et al. 1998]

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### Management:

\* *Venom Immunotherapy*: Venom immunotherapy is indicated in adults who have experienced a systemic reaction to an insect sting and who have positive skin test responses to one or more insects. Treatment is recommended for 3-5 years, after which the risk of anaphylaxis is estimated at 8-14%. Guidelines for the safe cessation of venom immunotherapy are still developing. Conversion from two positive skin tests to a negative result is an agreed upon criteria for stopping therapy. Roughly 20% of individuals convert to a negative skin test after 3-5 years of therapy. [*American Journal of Emergency Medicine*, Vol. 14, No. 4, July 1996]

• *Venom Immunotherapy for Fire Ants*: Whole body immunotherapy for fire ants consists of weekly subcutaneous injections, which may continue over a period of years. In patients who discontinued therapy after 2-19 years, 76% still had skin test sensitivity, but 94% had no reaction on receiving a sting.

• *Anaphylaxis and Immunotherapy*: Venom immunotherapy is generally well-tolerated. Approximately 6% of patients have treatment-related allergic reactions to the venom. The reactions tend to be mild and develop soon after initiation of treatment. Severe anaphylactic reactions to skin testing and allergen immunotherapy are rare, but do occur. In a national survey of allergists covering the period 1985-98, no deaths related to skin testing and 17 deaths related to allergy immunotherapy were reported. Sting-sensitive individuals who do not receive venom immunotherapy should receive instruction on avoidance and use of use of epinephrine emergency kits.

Literature review and abstract available.



# OTHER ALLERGY

ALL 1.4

Includes Latex, Radiocontrast Material, Vaccine, and Other Allergy.

## INFORMATION REQUIRED *Any history.*

### All Applicants:

- Report of Medical Examination to include the following:
  - Substance(s) to which allergic
  - Date of last reaction
  - Description of reaction to include description of angioedema and symptoms associated with respiratory or cardiovascular compromise.
  - Severity of reaction
  - Treatment to include resuscitative or life-support treatment if required.
  - Atopic history, i.e., triad of asthma, rhinitis, and chronic urticaria.
  - Recommendations for follow-up over the next 3 years.

### If Applicable:

- Copy of skin tests, challenge tests, and other diagnostic test reports.
- Copy of discharge summary for *all* related emergency room visits and hospitalizations.

CLEARANCE CRITERIA	REVIEWER	GUIDANCE
1. Mild or self-limited allergic reaction. Reaction <i>may include</i> one or more of the following symptoms: urticaria (hives), rash, pruritis (itching), flushing, or other hypersensitivity reaction, e.g., mild GI symptoms. 2. If reaction includes angioedema, edema does <i>not</i> cause airway obstruction, i.e., does <i>not</i> involve the neck, oropharynx (tongue, soft palate, lips), or larynx. 3. No significant circulatory (hypotension, syncope, shock) or respiratory (wheezing, SOB) compromise. 4. No anaphylactoid reaction or anaphylaxis, i.e., severe life-threatening allergic reaction. 5. No coexisting atopy, i.e., triad of chronic asthma, rhinitis, and urticaria.		
Meets clearance criteria 1-6, AND • Allergy: <u>Latex</u> .	RN	CLEAR  PCMO FOLLOW-UP Avoid use of latex (latex free products, e.g., gloves and condoms, required). Anaphylaxis kit required.
Meets clearance criteria 1-6, AND • Allergy: <u>Radiocontrast Material</u> .	RN	CLEAR  PCMO FOLLOW-UP Avoid radiocontrast material.
Meets clearance criteria 1-6, AND • Allergy: <u>Vaccine</u> .	MED ADVISOR	_____ Risk varies - assess based on detailed history.  PCMO FOLLOW-UP Avoid specific vaccine.
Meets clearance criteria 1-6, AND • Allergy: <u>Other Substance</u> .	MED ADVISOR	_____ Risk varies - assess based on detailed history.
Does not meet clearance criteria due to one or more of the following: • Reaction includes angioedema <i>with</i> associated airway obstruction, i.e., edema involves the neck, oropharynx (tongue, soft palate, lips), or larynx. • Coexisting atopy, i.e., triad of chronic asthma, rhinitis, and urticaria.	MED ADVISOR	_____ Risk varies - assess based on detailed history.

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## OTHER ALLERGY

Does not meet clearance criteria due to one or more of the following:

MED ADVISOR

DEFER/MNQ

- Reaction is severe or life-threatening (anaphylactoid or anaphylaxis), i.e., includes any of the following symptoms:
  - Significant respiratory compromise (bronchospasm, stidor, dyspnea, apnea) .
  - Significant cardiovascular compromise (hypotension, syncope, shock).
  - Loss of consciousness.
- Resuscitative or life support treatment required.

### DIAGNOSTIC CODES

- 995.2 Radiocontrast Material (allergic reaction)
- 995 Latex Allergy
- 995 Vaccine Allergy

Cross Reference ICD.9.CM

### NOTES AND INSTRUCTIONS FOR REVIEWERS:

#### Reviewers to Consider:

- Screening nurses should document intolerance to substance or hypersensitivity reaction, e.g., mild GI symptoms, on problem list if applicable.

### COMMENTS:

#### Definitions:

- **Anaphylaxis:** Immediate systemic reaction caused by rapid IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils. Clinically, the term anaphylaxis is used to describe a rapidly developing generalized reactions that may include pruritis, urticaria, angioedema (especially laryngeal edema), hypotension, wheezing and bronchospasm, nausea, vomiting, pain, diarrhea, uterine contractions, and/or direct cardiac effects, including arrhythmias.
- **Anaphylactoid reactions:** Immediate systemic reactions that are clinically similar to anaphylactic episodes but are not caused by an IgE-mediated immune response. One of the most common mechanisms of production of anaphylactoid reactions involves the direct (nonantigen-IgE) release of mediators from mast cells and basophils. This occurs in reactions to drugs and biologicals, most cases of idiopathic anaphylaxis, the majority of cases of exercise-induced anaphylaxis, and probably anaphylaxis from other physical factors, such as cold and sunlight. It may also be produced by chemical agents capable of causing mast cell degranulation, e.g., radiocontrast material or opiates.
- **Angioedema:** Edema extending into the deep dermis and subcutaneous tissue. The lesions of angioedema are large plaques (swollen and nonpitting), often on the eyelids, lips, palms, soles, or other parts of the face and extremities. Clinically it is characterized by swelling of the subcutaneous or submucosal tissue but without puritis. Involvement of the mucous membranes or the oropharynx may cause airway obstruction.
- **Urticaria (hives):** Raised, erythematous areas of edema involving only the superficial part of dermis. Urticaria lesions are typically localized raised swellings that are intensely itchy.

**Risk of Recurrence:** Major risk factors for recurrence of anaphylaxis include a prior history of such reactions, beta-adrenergic blocker or possibly ACE inhibitor therapy, and the multiple antibiotic sensitivity syndrome. Atopic background may be a risk factor for venom-and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to many medications.

*[The diagnosis and management of anaphylaxis. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology 1998 Aug;102(2):264 and 1998]*



## OTHER ALLERGY

**Symptoms:** Evaluation of symptoms should include the upper and lower airways (evidence of edema, stridor, dyspnea, wheezing, or apnea), the cardiovascular system (hypotension or syncope), the skin (urticaria, angioedema, or flushing), the gastrointestinal system (vomiting and diarrhea), and the state of consciousness. Signs and symptoms of potentially life-threatening anaphylaxis include stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmia, shock, seizures, and loss of consciousness. Such patients require immediate treatment.

### Frequency of Occurrence of Signs and Symptoms of Anaphylaxis

SIGNS/SYMPTOMS	PERCENT
Urticaria	88
Upper airway edema	56
Dyspnea, wheeze	47
Flush	46
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
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Seizure	1.5

**Atopy:** Atopic subjects appear to be predisposed to anaphylaxis and anaphylactoid reactions in general because they account for an inordinate percentage of cases in random series and in series of cases of idiopathic anaphylaxis, exercise-induced anaphylaxis, and anaphylactoid reactions to radiocontrast material. It is unclear why atopics exhibit a heightened predisposition. It is evident that increased levels of IgE and IgE mast cell interaction (as conventionally

**Death from Anaphylaxis:** Is usually due to respiratory obstruction and/or cardiovascular collapse. In patients dying from respiratory obstruction there is edema of the airway and pulmonary hyperinflation. Upper airway edema can be found in about 60% of deaths. Bronchial obstruction with hyperinflation of the lungs occurs in about half the cases. Bronchial obstruction is due to a combination of spasm, submucosal edema, and secretions. When death is due to cardiovascular collapse, there may be no postmortem findings. Myocardial damage, however, can be detected in the majority of cases.

### Vaccines:

- Anaphylactic reactions to vaccines are rare, and are attributed to egg proteins found in certain vaccines, and to other components (e.g., hydrolyzed gelatin, sorbitol, neomycin) in other vaccines.
- Current *measles and mumps* vaccines are produced in chick embryo fibroblast cultures which contain minute amounts of proteins that cross-react with eggs. Most reactions appear to be due to other components, e.g., gelatin or neomycin.
- *Yellow fever and influenza vaccines* are produced in embryonated eggs and contain more egg protein than do measles and mumps vaccines, raising concerns about giving these vaccines to individuals who have a history of anaphylaxis due to eggs. On rare occasions, these vaccines have caused anaphylactic reactions. Skin testing with yellow fever vaccines is recommended before administration to individuals with history of systemic anaphylactic symptoms after egg ingestion (generalized urticaria, hypotension, and/or manifestations of upper or lower airway obstruction). If the skin test is negative, the vaccine can be given. If it is positive, a desensitization protocol may be tried, though there is disagreement among experts about whether this is necessary. Skin testing with influenza vaccine has been used in children with a history of severe anaphylactic reactions to eggs. However, the recommendation is not to vaccinate such children, in view of the need for annual vaccination and the potential risk. (No comparable information on adult influenza vaccination was found in the material reviewed.) [Nicklas et al. 1998]
- *RabAvert* vaccines for rabies also is contraindicated in individuals allergic to egg and egg protein. [Nicklas et al. 1998]

**Latex:** Latex sensitivity has emerged as a problem over the last several decades, with increased use of latex products, which number in the thousands. Health care workers and others with occupational exposure to latex are at higher risk of reactions than the general public, although the condition can develop in anyone, particularly atopic individuals.

Exposure to latex may be by direct contact, parenteral administration, or aerosol (e.g., from powdered latex gloves when latex components are absorbed onto cornstarch powder particles, which are then inhaled). Mucosal contact and parenteral administration pose the greatest risk for anaphylaxis and can cause life-threatening reactions in individuals.

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with previous mild cutaneous or respiratory reactions. Patients with diagnosed latex allergy by history or skin testing should wear a medical identification bracelet, carry a medical identification card, or both. Patients may also be instructed to carry epinephrine and antihistamines for self-administration.

Skin prick tests should be considered for patients who are at risk or have a history suggestive of latex sensitivity. All individuals with identified latex sensitivity should have all medical/surgical/dental procedures performed in a latex-controlled environment, which is defined as an environment in which no latex gloves or accessories (catheters, adhesives, tourniquets, and anesthesia equipment) come into contact with the patient. [Nicklas et al. 1998]

**Radiographic contrast material (RCM):** Radiographic contrast material that is used extensively in radiologic examinations, induces adverse reactions of all types in about 5-8% of individuals, including some anaphylactoid reactions. Life-threatening reactions occur in <0.1% with conventional (high osmolality) RCM. The risk of a second anaphylactoid reaction is estimated at 16-44% if no precautions are taken. Newer (low osmolality) agents appear to reduce the risk of anaphylactoid reactions to about 1/5 of those with conventional agents. Patients who have had an anaphylactoid reaction to RCM should avoid these materials, if possible. If their use is necessary, the patient may be pretreated (usually with oral glucocorticosteroids, H1 and H2 antihistamines, and other medications such as ephedrine), and low osmolar RCM should be used. [Nicklas et al. 1998]

Literature review available.



# EXERCISE, COLD, HEAT & STRESS INDUCED URTICARIA AND ANGIOEDEMA

ALL 2.1

Includes Exercise, Cold, Heat, and Stress Induced Anaphylaxis.

For Exercise Induced Asthma; See "Asthma" Guideline.

## INFORMATION REQUIRED *Any history.*

### All Applicants:

- Report of Medical Examination to include the following:
  - Precipitating factors
  - Date(s) of last reaction(s)
  - Description of reaction(s) to include description of angioedema and symptoms associated with respiratory or cardiovascular compromise
  - Frequency of reactions
  - Severity of reaction
  - Treatment to include resuscitative or life-support treatment if required.
  - Atopic history, i.e., triad of asthma, rhinitis, and chronic urticaria.
  - Recommendations for follow-up over the next 3 years.

### If Applicable:

- Copy of skin tests, challenge tests, and other diagnostic test reports.
- Copy of discharge summary for *all* related emergency room visits and hospitalizations.

## CLEARANCE CRITERIA

## REVIEWER

## GUIDANCE

1. Mild or self-limited allergic reaction. Reaction *may include* one or more of the following symptoms: urticaria (hives), rash, pruritis (itching), flushing, or other hypersensitivity reaction, e.g., mild GI symptoms.
2. If reaction includes angioedema, edema does *not* cause airway obstruction, i.e., does *not* involve the neck, oropharynx (tongue, soft palate, lips), or larynx.
3. No significant circulatory (hypotension, syncope, shock) or respiratory (wheezing, SOB) compromise.
4. No anaphylactoid reaction or anaphylaxis, i.e., severe life-threatening allergic reaction.
5. No resuscitative or life support treatment required.
6. No coexisting atopy, i.e., triad of chronic asthma, rhinitis, and urticaria.

### Meets clearance criteria 1-6, AND

- \* If symptoms require treatment, symptoms well controlled with antihistamines or hydroxyzine (Attarx).

RN

CLEAR

### Does not meet clearance criteria due to one or more of the following:

- Symptoms poorly controlled, or require treatment with medication other than antihistamines or hydroxyzine (Attarx), i.e., steroids.
- Reaction includes angioedema *with* associated airway obstruction, i.e., edema involves the neck, oropharynx (tongue, soft palate, lips), or larynx.
- Coexisting atopy, i.e., triad of chronic asthma, rhinitis, and urticaria.

MED ADVISOR

Risk varies - assess based on detailed history.

### Does not meet clearance criteria due to one or more of the following:

- Reaction is severe or life-threatening (anaphylactoid or anaphylaxis), i.e., includes any of the following symptoms:
  - Significant respiratory compromise (bronchospasm, asthma, wheezing, SOB)
  - Significant cardiovascular compromise (hypotension, syncope, shock).
  - Loss of consciousness.
- Resuscitative or life support treatment required.

MED ADVISOR

DEFERRED

## EXERCISE, COLD, HEAT & STRESS INDUCED URTICARIA AND ANGIOEDEMA

### DIAGNOSTIC CODES

708.2 Cold/Heat Induced Urticaria  
995.1 Angioedema with Urticaria  
995.0 Anaphylaxis

Cross Reference ICD.9.CM

### NOTES AND INSTRUCTIONS FOR REVIEWERS:

#### Reviewers to Consider:

- None

### COMMENTS:

#### Definitions:

- Anaphylaxis: Immediate systemic reaction caused by rapid IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils. Clinically, the term anaphylaxis is used to describe a rapidly developing generalized reaction that may include pruritus, urticaria, angioedema (especially laryngeal edema), hypotension, wheezing and bronchospasm, nausea, vomiting, pain, diarrhea, uterine contractions, and/or direct cardiac effects, including arrhythmias.
- Anaphylactoid reactions: Immediate systemic reactions that are clinically similar to anaphylactic episodes but are not caused by a IgE-mediated immune response. One of the most common mechanisms of production of anaphylactoid reactions involves the direct (nonantigen-IgE) release of mediators from mast cells and basophils. This occurs in reactions to drugs and biologicals, most cases of idiopathic anaphylaxis, the majority of cases of exercise-induced anaphylaxis, and probably anaphylaxis from other physical factors, such as cold and sunlight. It may also be produced by chemical agents capable of causing mast cell degranulation, e.g., radiocontrast material or opiates.
- Angioedema: Edema extending into the deep dermis and subcutaneous tissue. The lesions of angioedema are large plaques (swollen and nonpitting), often on the eyelids, lips, palms, soles, or other parts of the face and extremities. Clinically it is characterized by swelling of the subcutaneous or submucosal tissue but without puritis. Involvement of the mucous membranes or the oropharynx may cause airway obstruction.
- Urticaria (hives): Raised, erythematous areas of edema involving only the superficial part of dermis. Urticaria lesions are typically localized, raised, swellings that are intensely itchy.

**Symptoms:** Evaluation of symptoms should include the upper and lower airways (evidence of edema, stridor, dyspnea, wheezing, or apnea), the cardiovascular system (hypotension or syncope), the skin (urticaria, angioedema, or flushing), the gastrointestinal system (vomiting and diarrhea), and the state of consciousness. Signs and symptoms of potentially life-threatening anaphylaxis include stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmia, shock, seizures, and loss of consciousness. Such patients require immediate treatment.

#### Frequency of Occurrence of Signs and Symptoms of Anaphylaxis

SIGNS/SYMPTOMS	PERCENT
Urticaria and angioedema	88
Upper airway edema	56
Dyspnea, wheeze	47
Flush	46
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Headache	15
Rhinitis	16
Substernal pain	6
Itch without rash	4.5
Seizure	1.5



## EXERCISE, COLD, HEAT & STRESS INDUCED URTICARIA AND ANGIOEDEMA

**Risk of Recurrence:** Major risk factors for recurrence of anaphylaxis include a prior history of such reactions, beta-adrenergic blocker or possibly ACE inhibitor therapy, and the multiple antibiotic sensitivity syndrome. Atopic background may be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to many medications.

*[The diagnosis and management of anaphylaxis. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology 1998 Aug;102(2):264 and 1998]*

**Atopy:** Atopic subjects appear to be predisposed to anaphylaxis and anaphylactoid reactions in general because they account for an inordinate percentage of cases in random series and in series of cases of idiopathic anaphylaxis, exercise-induced anaphylaxis, and anaphylactoid reactions to radiocontrast material. It is unclear why atopics exhibit a heightened predisposition. It is evident that increased levels of IgE and IgE mast cell interaction (as conventionally understood) cannot account for this phenomenon. *[Middleton: Allergy: Principles and Practice, 5th ed., 1998]*

**Death from Anaphylaxis:** Is usually due to respiratory obstruction and/or cardiovascular collapse. In patients dying from respiratory obstruction there is edema of the airway and pulmonary hyperinflation. Upper airway edema can be found in about 60% of deaths. Bronchial obstruction with hyperinflation of the lungs occurs in about half the cases. Bronchial obstruction is due to a combination of spasm, submucosal edema, and secretions. When death is due to cardiovascular collapse, there may be no postmortem findings. Myocardial damage, however, can be detected in the majority of cases.

### Physical Urticaria - Exacerbating Factors:

- Warm, humid environment
- Cold environment
- Ingestion of food within 2-4 hours before exercise
- Emotional stress
- Time of menses in females (19% in one survey) *[Briner & Sheffer 1992]*
- Prior exposure to known allergens (in addition to foods) *[Briner & Sheffer 1992]*
- Aspirin and NSAIDs *[Briner & Sheffer 1992]*

**Exercise-Induced Urticaria:** Also called "cholinergic urticaria," the trigger is an increase in core body temperature, which may be due to exercise, but also may occur with fever, emotional stress, or a hot bath. Major manifestations are limited to the skin; rarely, anaphylaxis occurs in rare cases, and consists of 2-4 mm punctate wheals surrounded by a red flare. Other symptoms include lacrimation, salivation, and diarrhea. Urticaria usually appears about 6 minutes after beginning exercise and increases for 12-25 minutes thereafter. Initial episodes generally occur in the first 2-3 years of life and can recur for many years. Symptoms are usually reproducible with each period of exercise or other stimulus. *[Volcheck & Li, 1997]*

**Treatment:** Treatment is symptomatic. No prophylactic therapy for either condition has proven effective. Attempts at preventing exercise-induced anaphylaxis, using e.g., H1 and H2 antagonists have generally been unsuccessful. *[Briner & Sheffer 1992; 1993]*

First-line treatment for an attack is usually an H1-receptor antagonist, particularly hydroxyzine. A second H1 receptor antagonist or an H2 antagonist can be added if symptoms are not controlled. *[Volcheck & Li 1997]* For those with food dependent conditions, particular foods should be avoided (or all foods) 2-4 hours before exercising. Patients should be encouraged to stop exercising as soon as symptoms appear and to carry an epinephrine kit and benadryl for use as soon as symptoms appear.

**Exercise-Induced Anaphylaxis:** This condition is induced only by exercise, but it occurs only variably in most patients, i.e., it is not reproducible with each bout of exercise. Cutaneous symptoms occur first, usually consisting of pruritis and erythema, accompanied by fatigue and generalized warmth. The progression is then to urticaria and eventually angioedema. In most patients (90%), the urticaria form giant-sized wheals (10-15 mm in diameter), which differ from the smaller, punctate lesions of exercise-induced urticaria. *[Briner & Sheffer 1992]* Vascular collapse may ensue, with or without the development of angioedema. Choking, respiratory stridor, gastrointestinal colic, and nausea and vomiting may occur in severe attacks. Headaches, lasting up to 3 days, are sometimes late sequelae. One death, out of about 1,000 reported cases, has been attributed to exercise-induced anaphylaxis. *[Volcheck & Li 1997]*

In a subset of patients, the condition only occurs within about 2-4 hours after ingestion of certain foods (or in some individuals, any solid food). Foods that have been implicated include shellfish, wheat, raw celery, cabbage, peaches, grapes, chicken, hazelnuts, and apples. In these patients, neither the food alone nor exercise alone will trigger an attack. The first attack may occur at any age, but the mean age is in the 20's. *[Volcheck & Li 1997]*



## EXERCISE, COLD, HEAT & STRESS INDUCED URTICARIA AND ANGIOEDEMA

**Cold and Heat Induced Urticaria and Angioedema:** The development of wheals after exposure to cold can occur in several clinical situations, including secondary cold urticaria, familial cold urticaria, and essential acquired cold urticaria. The latter has been reported to cause 96% of cold urticaria and develops most often in young adults. Not infrequently, the onset follows emotional stress, viral illness, or multiple insect bites. Wheals develop within minutes upon rewarming of the involved sites. Mucous membranes or the tongue may be affected. A change in skin temperature, not absolute skin temperature, is important for the generation of the lesions. Bronchospasm, angioedema, hypotension, flushing, and even drowning on cold water exposure have been reported.

**Treatment:** The cardinal objective of cold urticaria management is the prevention of shock reactions during aquatic and other cold-temperature exposures. Antihistamines administered 30 to 60 minutes before cold exposure have been effective in aborting urticarial episodes in most. Cyproheptadine HCl (2-4 mg three times a day) has been the treatment of choice for patients with cold urticaria. Besides its H1 antihistamine action, cyproheptadine has antiserotonin, anticholinergic, and H2 antihistaminic activity. Doxepin (a most effective H1 - and H2 -receptor antagonist) also effectively suppresses cold urticaria. Doxepin can be started at 10 mg at bedtime and then gradually increased to 10 to 25 mg three times a day. Neither beta-agonists nor prednisone have been beneficial for the treatment of cold urticaria. Desensitization, although not without risk, has been shown to be beneficial if carefully performed.

**Cholinergic (Stress Included) Urticaria and Angioedema:** Second to dermatographism, this condition has been reported to be the most common of the physical urticaria. The lesions are most distinctive, characterized by small, 2- to 3-mm scattered wheals surrounded by large, erythematous flares. Most patients are adolescents and young adults. Lesions are extremely pruritic and may affect the entire body except for the palms, soles, and axilla. Precipitating stimuli include exercise, warm temperatures, ingestion of hot or spicy foods, and emotional stress. The condition often remits within several years, but cases lasting for more than 20 to 30 years have been reported.

**Treatment:** Attacks of cholinergic urticaria can be aborted by the prompt application of cold water or ice to the skin after the induction of sweating. A refractory period of up to 24 hours can be induced by a carefully taken hot bath. Cholinergic urticaria responds better to hydroxyzine than do the other physical urticarias.

Literature review and abstract available.



# CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

ALL 2.2

Includes Idiopathic Anaphylaxis.

## INFORMATION REQUIRED *Any history...*

### All Applicants:

- Report of Medical Examination
  - Precipitating factors
  - Date(s) of last reaction(s)
  - Description of reaction(s) to include description of angioedema and symptoms associated with respiratory or cardiovascular compromise.
  - Severity of reaction
  - Treatment to include resuscitative or life-support treatment if required.
  - Treatment
  - Current status
  - Recommendations for follow-up over the next 3 years.

### If Applicable:

- Copy of skin tests, challenge tests, and other diagnostic test reports.
- Copy of discharge summary for *all* related emergency room visits and hospitalizations.

CLEARANCE CRITERIA	REVIEWER	GUIDANCE
<ol style="list-style-type: none"> <li>1. Symptoms, when present, do not significantly interfere with activities of daily living.</li> <li>2. Mild or self-limited allergic reaction. Reaction <i>may include</i> one or more of the following symptoms: urticaria (hives), rash, pruritis (itching), flushing, or other hypersensitivity reaction, e.g., mild GI symptoms.</li> <li>3. If reaction includes angioedema, edema does <i>not</i> cause airway obstruction, i.e., does <i>not</i> involve the neck, oropharynx (tongue, soft palate, lips), or larynx.</li> <li>4. Reaction is <i>not</i> severe or life-threatening (anaphylactoid or anaphylaxis), i.e., does <i>not</i> include any of the following symptoms:                             <ul style="list-style-type: none"> <li>• Significant respiratory compromise (bronchospasm, stidor, dyspnea, apnea) .</li> <li>• Significant cardiovascular compromise (hypotension, syncope, shock).</li> <li>• Loss of consciousness.</li> </ul> </li> <li>5. No resuscitative or life support treatment required.</li> <li>6. No coexisting atopy, i.e., triad of chronic asthma, rhinitis, and urticaria.</li> <li>7. No need for oral or injectable steroids.</li> </ol>		
<b>Meets clearance criteria 1-7, AND</b> <ul style="list-style-type: none"> <li>• If symptoms require treatment, well controlled with antihistamines or hydroxyzine (Attarx).</li> </ul>	RN	CLEAR
<b>Does not meet clearance criteria due to one or more of the following:</b> <ul style="list-style-type: none"> <li>• Symptoms poorly controlled, or require treatment with medication other than antihistamines or hydroxyzine (Attarx), i.e., steroids.</li> <li>• Reaction includes angioedema <i>with</i> associated airway obstruction, i.e., edema involves the neck, oropharynx (tongue, soft palate, lips), or larynx.</li> <li>• Coexisting atopy, i.e., triad of chronic asthma, rhinitis, and urticaria.</li> </ul>	MED ADVISOR	_____ Risk varies - assess based on detailed history.

(continued on next page)

## CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

<p>Does not meet clearance criteria due to one or more of the following:</p> <ul style="list-style-type: none"> <li>• Reaction is severe or life-threatening (anaphylactoid or anaphylaxis), i.e., includes any of the following symptoms: <ul style="list-style-type: none"> <li>- Significant respiratory compromise (bronchospasm, stidor, dyspnea, apnea).</li> <li>- Significant cardiovascular compromise (hypotension, syncope, shock).</li> <li>- Loss of consciousness.</li> </ul> </li> <li>• Resuscitative or life support treatment required.</li> </ul>	MED ADVISOR	DEFER/MNQ
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### DIAGNOSTIC CODES

708.1 Idiopathic Urticaria  
708.8 Chronic Urticaria  
995.1 Angioedema with Urticaria  
995.0 Anaphylaxis

Cross Reference ICD.9.CM

### NOTES AND INSTRUCTIONS FOR REVIEWERS:

#### Reviewers to Consider:

- None

### COMMENTS:

#### Definitions:

- Anaphylaxis: Immediate systemic reaction caused by rapid IgE-mediated immune release of potent mediators from mast cells and basophils. Anaphylaxis is used to describe a rapidly developing generalized reactions that may include pruritis, urticaria, angioedema (especially laryngeal edema), hypotension, wheezing and bronchospasm, nausea, vomiting, pain, diarrhea, uterine contractions, and/or direct cardiac effects, including arrhythmias.
- Anaphylactoid reactions: Immediate systemic reactions that are clinically similar to anaphylactic episodes but are not caused by an IgE-mediated immune response. One of the most common mechanisms of production of anaphylactoid reactions involves the direct (nonantigen-IgE) release of mediators from mast cells and basophils. This occurs in reactions to drugs and biologicals, most cases of idiopathic anaphylaxis, the majority of cases of exercise-induced anaphylaxis, and probably anaphylaxis from other physical factors, such as cold and sunlight. It may also be produced by chemical agents capable of causing mast cell degranulation, e.g., radiocontrast material or opiates.
- Angioedema: Edema extending into the deep dermis and subcutaneous tissue. The lesions of angioedema are large plaques (swollen and nonpitting), often on the eyelids, lips, palms, soles, or other parts of the face and extremities. Clinically it is characterized by swelling of the subcutaneous or submucosal tissue but without pruritis. Involvement of the mucous membranes or the oropharynx may cause airway obstruction.
- Urticaria (hives): Raised, erythematous areas of edema involving only the superficial part of dermis. Urticaria lesions are typically localized, raised, swellings that are intensely itchy.

**Risk of Recurrence:** Major risk factors for recurrence of anaphylaxis include a prior history of such reactions, beta-adrenergic blocker or possibly ACE inhibitor therapy, and the multiple antibiotic sensitivity syndrome. Atopic background may be a risk factor for venom- and latex-induced anaphylaxis and possibly anaphylactoid reactions to radiographic contrast material but not for anaphylactic reactions to many medications.

*[The diagnosis and management of anaphylaxis. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology 1998 Aug;102(2):264 and 1998]*



## CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

**Symptoms:** Evaluation of symptoms should include the upper and lower airways (evidence of edema, stridor, dyspnea, wheezing, or apnea), the cardiovascular system (hypotension or syncope), the skin (urticaria, angioedema, or flushing), the gastrointestinal system (vomiting and diarrhea), and the state of consciousness. Signs and symptoms of potentially life-threatening anaphylaxis include stridor, respiratory distress, wheezing, hypotension, cardiac arrhythmia, shock, seizures, and loss of consciousness. Such patients require immediate treatment.

### Frequency of Occurrence of Signs and Symptoms of Anaphylaxis

SIGNS/SYMPTOMS	PERCENT
Urticaria and angioedema	88
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Flush	46
Dizziness, syncope, hypotension	33
Nausea, vomiting, diarrhea, cramping abdominal pain	30
Headache	15
Rhinitis	16
Substernal pain	6
Itch without rash	4.5
Seizure	1.5

**Atopy:** Atopic subjects appear to be predisposed to anaphylaxis and anaphylactoid reactions in general because they account for an inordinate percentage of cases in random series and in series of cases of idiopathic anaphylaxis, exercise-induced anaphylaxis, and anaphylactoid reactions to radiocontrast material. It is unclear why atopics exhibit a heightened predisposition. It is evident that increased levels of IgE and IgE mast cell interaction (as conventionally understood) are not sufficient alone to account for this phenomenon. [Middleton: *Allergy: Principles and Practice*, 5th ed., 1998]

**Death from Anaphylaxis:** Is usually due to respiratory obstruction and/or cardiovascular collapse. In patients dying from respiratory obstruction there is edema of the airway and pulmonary hyperinflation. Upper airway edema can be found in about 60% of deaths. Bronchial obstruction with hyperinflation of the lungs occurs in about half the cases. Bronchial obstruction is due to a combination of spasm, submucosal edema, and secretions. When death is due to cardiovascular collapse, there may be no postmortem findings. Myocardial damage, however, can be detected in the majority of cases.

**Chronic Idiopathic Urticaria and Angioedema:** Urticaria and angioedema are classified as acute or chronic, based on whether the episodes persist for more or less than 6 to 8 weeks. Chronic urticaria and angioedema of 6 weeks' duration or longer are considered to be idiopathic in 80% to 95% of cases. The mean duration is 6 months, although this cutaneous condition may persist for several years. Forty percent of the cases with chronic idiopathic urticaria (CIU) experience only urticaria; 49% have both urticaria and angioedema, and the remaining 11% have only angioedema.

**Clinical Evaluation:** The possibility of an adverse or allergic reaction to venom, food, or a drug is always considered in the patient presenting with urticaria and angioedema. If a comprehensive clinical evaluation is indeterminate, a cost-effective laboratory work-up is needed. After a complete cognitive review of the clinical information and laboratory data other immunologic studies may be ordered, although these tests are rarely required in an otherwise healthy individual with only the cutaneous manifestations of urticaria and angioedema (as is the case with chronic idiopathic urticaria and angioedema). Hidden food and food additive sensitivities are frequently considered as a cause of hives by the patient, but rarely can such a relationship between food and urticaria be established.

**Treatment:** With chronic urticaria and angioedema, avoidance of potentiating factors such as alcoholic beverages, heat, emotional stress, aspirin, and exertion is advocated. The treatment of this condition is generally considered palliative rather than curative. Long-term treatment is the rule for patients with chronic urticaria and angioedema; therefore, careful selection of therapy is mandatory in order to maximize the benefit without resulting in severe drug side effects. Because most chronic urticaria is idiopathic, the physician should dispel patients' unrealistic expectations, if any, and reassure them that the prognosis is good and spontaneous remission is anticipated.

**H1 antihistamines:** Antihistamines are the mainstay of symptomatic management, mainly for pruritus. The diversity of mediators produced and the variety of inflammatory cells involved in urticarial reactions explain why antihistamines do not completely eliminate all the signs and symptoms of chronic urticaria. Sedation is common with most of the classic H1



## CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

antagonists. The patient's tolerance for this side effect and others, such as dry mouth, urinary retention, and blurred vision, will dictate the maximum antihistamine dose to be utilized. The limiting nature of the side effects of the classic antihistamines may not allow optimal control of the hives. There are six groups of classic H1 antihistamines. The newer category of less sedating antihistamines, terfenadine, loratadine, and cetirizine (Zyrtec) are not necessarily more effective, but compliance improves when drugs are easy to take and no symptomatic adverse effects are experienced.

Zyrtec is the only antihistamine with an indication for chronic idiopathic urticaria. Hydroxyzine (Atarax) is traditionally first-line treatment for chronic idiopathic urticaria, and it remains the standard to which all other antihistamines are compared. When choosing two antihistamines for the patient with the more difficult chronic urticaria, choose from different groups. The combination of hydroxyzine and cyproheptadine is particularly effective. A popular combination is a nonsedating antihistamine in the morning and a sedating antihistamine, such as hydroxyzine, at bedtime. Patients with chronic urticaria should not be managed with as needed antihistamines exclusively, as this therapeutic rationale does not approach the problem from a preventive standpoint. Once an effective dose schedule is established with an antihistamine, the total dose can be gradually reduced according to the schedule until the lowest effective dose is found or the drug is withdrawn.

**H2 antihistamines:** The patient with inadequate symptomatic control on an H1 or combination of H1 antihistamines at the highest tolerated or recommended dose should be prescribed an H2 antihistamine. Cimetidine, 300 mg four times daily, or ranitidine, 150 mg twice daily can be combined with an H1 antihistamine. H2 receptors make up about 10% to 15% of the total number of histamine receptors in the cutaneous vasculature. The H2 antihistamine should be discontinued after 3 to 4 weeks if there is no definitive clinical benefit.

**Doxepin:** Doxepin, a heterocyclic variant of amitriptyline, is approximately 800 times more potent than diphenhydramine in vitro on a molar basis, and doxepin is six times more potent than cimetidine. Clinical efficacy for doxepin in the management of chronic idiopathic urticaria has been established in doses ranging from 30 to 150 mg/day. Doxepin is now considered a first-line treatment for chronic idiopathic urticaria.

**Corticosteroids:** Corticosteroids are very effective in suppressing most signs and symptoms of all categories of urticaria. The physical urticarias (excluding delayed pressure urticaria/angioedema) are the exception. Corticosteroids should be judiciously prescribed only in severe chronic urticaria and for uncontrolled exacerbations of urticaria and angioedema. Their exact pharmacologic action is not completely understood. The patient should be tapered off the corticosteroids, with complete withdrawal of the drug prior to the onset of significant side effects as the desirable objective. An alternate-day regimen of corticosteroids, prednisone 25 to 40 mg or equivalent dose of methylprednisolone, is used in the management of the patient with steroid-dependent chronic urticaria to maintain a clinical remission. Several months of therapy may be required. Corticosteroid-sparing agents and alternative drugs have been reported in the

management of severe chronic idiopathic urticaria. Methotrexate seems to hold promise as further experience with this agent is gained. Unique therapies, psoralen plus ultraviolet A light (PUVA) treatments, and intravenous gamma globulin infusions have been reported to help some patients. [Roger W. Fox, MD, *Current Practice of Medicine* 1998, 1:141-150.]

**Idiopathic Anaphylaxis:** Idiopathic anaphylaxis is rare, and is a diagnosis of exclusion. In total, somewhat more than 350 patients have been reported with this condition, most by one group of investigators. In addition to typical anaphylactic symptoms, individuals with this condition often become very apprehensive.

Patients should receive intensive evaluation, including a meticulous history of the events surrounding episodes of anaphylaxis. Clinical evaluation to exclude an underlying systemic disorder (e.g., systemic mast cell disease or acquired/hereditary angioedema) should also be carried out. Selective testing for specific IgE antibodies may also pinpoint a cause in some instances.

Individually tailored prophylactic protocols are the norm, and may include corticosteroids, beta-agonists, and antihistamines. Education and support of patients is essential. [Nicklas et al. 1998]

Literature review and abstract available.



## RHINITIS (ALLERGIC AND NON-ALLERGIC)

ALL 3.1

Includes Seasonal ("Hay Fever"), Perennial, and Intermittent Allergic Rhinitis.

For Reactive Airway Symptoms; See "Asthma" Guideline.

### INFORMATION REQUIRED *Any history.*

#### All Applicants:

- Report of Medical Examination to include the following:
  - Allergen(s), if known
  - Description of symptoms
  - Frequency of symptoms
  - Severity of symptoms
  - Treatment, to include immunotherapy (immunotherapy must be completed by applicants departure date).
  - Recommendations for follow-up over the next 3 years.

#### If Applicable:

- Copy of skin tests, challenge tests, and other diagnostic test reports.
- Copy of immunotherapy report (not mandatory for allergic and non allergic rhinitis).
- Copy of discharge summary for *all* related emergency room visits and hospitalizations.

CLEARANCE CRITERIA	REVIEWER	GUIDANCE
<ol style="list-style-type: none"><li>1. Allergic or Non Allergic Rhinitis; May be described as one or more of the following:<ul style="list-style-type: none"><li>• Seasonal rhinitis or "Hay Fever"</li><li>• Perennial rhinitis</li><li>• Intermittent rhinitis</li><li>• Environmental allergy</li></ul></li><li>2. Common allergens or "triggers" include grass, ragweed, tree pollens, dust or dust mites, fungal spores, animal dander, hair, feathers, wool, plants, flowers, perfume, and smoke.</li><li>3. Symptoms well controlled with allergen avoidance, decongestants, antihistamines, or nasal steroids.</li><li>4. No coexisting asthma.</li><li>5. No coexisting atopy, i.e., triad of asthma, rhinitis, and chronic urticaria.</li><li>6. No need for oral or injectable steroids.</li></ol>		
<b>Meets clearance criteria 1-6, AND</b> <ul style="list-style-type: none"><li>• If history of immunotherapy, course of therapy complete.</li></ul> <i>Note: Immunotherapy must be completed by applicants tentative date of departure for country.</i>	<b>RN</b>	<b>CLEAR</b>
<b>Does not meet clearance criteria due to one or more of the following:</b> <ul style="list-style-type: none"><li>• Ongoing immunotherapy, i.e., will <i>not</i> be complete by applicants tentative date of departure.</li></ul>	<b>RN</b>	<b>DEFER</b> Until immunotherapy complete.
<b>Does not meet clearance criteria due to one or more of the following:</b> <ul style="list-style-type: none"><li>• Symptoms poorly controlled, or require treatment with medication other than antihistamines or hydroxyzine (Attarx), i.e., steroids.</li><li>• Coexisting asthma.</li><li>• Coexisting atopy, i.e., triad of asthma, rhinitis, and chronic urticaria.</li><li>• Need for oral or injectable steroids.</li></ul>	<b>MED ADVISOR</b>	Risk varies - assess based on detailed history.



## RHINITIS (ALLERGIC AND NON ALLERGIC),

### DIAGNOSTIC CODES

#### Allergy (Allergic Reaction)

- 477.8 Animal Dander, Animal Hair, Dust, Feathers,
- 477.0 Grass, Pollen, Ragweed
- 477.9 Airborne Substance

Cross Reference ICD.9.CM

### NOTES AND INSTRUCTIONS FOR REVIEWERS:

#### Reviewers to Consider:

- None

### COMMENTS:

**Background:** Allergic rhinitis affects between 15 and 20% of the U.S. population, thereby qualifying it as one of the most common chronic diseases. Even though the incidence can rise temporarily age, with rhinitis on patients report symptoms before the age of 30 years, with a peak incidence in childhood and adolescence. It is seen infrequently in old age. Complications of chronic rhinitis include chronic and recurrent sinusitis, chronic cough, otitis, nasal polyposis, and sleep disturbance. There is also convincing evidence that untreated allergic rhinosinusitis worsens asthma. Allergic rhinitis is associated with a genetic predisposition for atopic disease. Persons with one atopic parent have a 30% chance of developing allergic rhinitis. If both parents have allergies, this increases to 50%. [Rakel: Conn's Current Therapy, 1999]

**Progression, Recurrence:** Allergic rhinitis symptoms are common and persistent in the first four decades of life, and symptoms usually improve after age 50. Symptoms resolve within 5 years in only 5% to 10% of patients; individuals with mild seasonal allergic rhinitis are most likely to have remissions. Early onset of rhinitis indicates a very high probability of allergic etiology. Of patients whose chronic rhinitis begins before the age of 10 years, 90% have allergic disease. In contrast, of patients whose rhinitis begins after age 40, a nonallergic etiology is diagnosed in close to 60%. [Primary Care; Clinics in Office Practice Volume 25 • Number 3 • September 1998]

**Seasonal Allergic Rhinitis:** In seasonal allergic rhinitis (hay fever or rose fever), there is a temporal relationship between exposure to particular antigens, usually grass or ragweed pollen and/or molds, and the occurrence of symptoms. Seasonal allergies are caused by inhaled airborne pollens. In the United States, trees tend to pollinate in the spring, grasses pollinate during late spring and summer, and weeds pollinate in fall (hay fever). The action of these pollens on the target areas of the respiratory tract produces the profuse watery nasal discharge and associated irritation.

**Perennial Allergic Rhinitis:** Perennial (year round) allergic rhinitis is more insidious, with symptoms of a chronic nature and a few flares. The most important perennial allergens are indoor allergens such as house dust mites, pets (dogs, cats, and other furred animals), cockroaches, and molds. It is easy to attribute the symptoms to other causes and underestimate the importance of common allergens in the environment that truly provoke the symptoms. [Medical Clinics of North America Volume 83 • Number 1 • January 1999]

**Non-allergic Rhinitis with Eosinophilia Syndrome (NARES):** Disease associated with a nasal smear showing abundant eosinophils, but allergy skin testing is negative. Patients do not respond well to antihistamines and are treated with topical corticosteroids.

#### Diagnostic Clues to Differentiate Allergic from Non allergic Rhinitis

- Temporal relationship between symptom onset, duration, and seasonal or environmental changes (moving to a new location, acquiring a pet) is suggestive of allergic rhinitis
- Sneezing, nasal pruritus, and associated conjunctival symptoms are characteristic of allergic rhinitis
- Allergic triggers (pollen, dust, molds, pets) suggest allergic rhinitis; nonspecific irritants (perfumes, tobacco smoke, cold or dry air) suggest nonallergic disease
- Age at onset: The earlier the onset, the more likely that allergies are involved
- Personal or family history of rhinitis, asthma, or eczema: more likely to identify patients with allergic rhinitis



## RHINITIS (ALLERGIC AND NON ALLERGIC)

**Treatment:** The three treatment modalities to consider are (1) avoidance, (2) pharmacotherapy, and (3) immunotherapy. Avoidance is the first step that should be initiated after identification of the offending allergens. Complete avoidance of pollens is difficult; however, minimizing outdoor activities during the peak season of a particular allergen can be helpful. Antihistamines are a reasonable choice for use as first-line agents in the treatment of intermittent or mild symptoms of allergic rhinoconjunctivitis. In moderate or severe disease, they can be useful adjunctive agents in therapy with topical corticosteroids or cromolyn sodium.

**Atopic:** The atopic state runs in families and is genetically transmitted. Atopic individuals produce increased amounts of immunoglobulin E (IgE), a type of antibody which binds particularly avidly to mast cells. These cells are located throughout the body and release histamine and other inflammatory agents when triggered by the allergen. The common atopic conditions are allergic rhinitis, allergic (atopic) asthma, and immediate (IgE-mediated) reactions to foods.

**Allergen Immunotherapy:** Immunotherapy is the only therapy for allergic rhinitis that entails a theoretical cure. This involves the administration of specific allergens in escalating doses until a target dose (maintenance) is reached. Administration is usually subcutaneous. Approximately 80% of patients have symptomatic improvement with... immunotherapy. It is not clear, however, what this percentage is among patients who have failed all other treatments.

Literature review available.